STN-STRUCTURE SEARCH
9.22.04

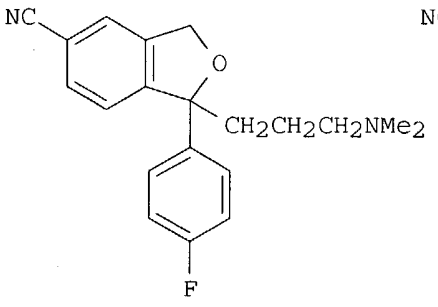
10/750,049

=> d ibib abs hitstr 1-29

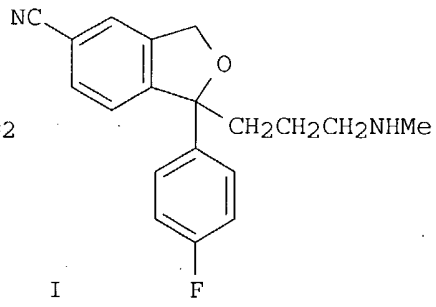
L10 ANSWER 1 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:691476 CAPLUS
DOCUMENT NUMBER: 141:207048
TITLE: Preparation of pure citalopram
INVENTOR(S): Kaushik, Vipin Kumar; Rao, Divvela Venkata Naga Srinivasa; Handa, Vijay Kumar; Sivakumaran, Meenakshisunderam
PATENT ASSIGNEE(S): Aurobindo Pharma Ltd., India
SOURCE: U.S., 3 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6781003	B1	20040824	US 2003-456135	20030609
PRIORITY APPLN. INFO.:			US 2003-456135	20030609

GI



I



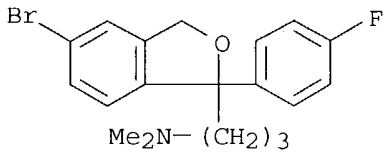
II

AB The present invention relates to an industrially advantageous method for the purification of citalopram (I) wherein desmethyl citalopram (II), present in crude citalopram as an impurity, is methylated to produce pure citalopram I. The resulting citalopram product I is isolated as the base or a pharmaceutically acceptable salt thereof. Thus, to crude citalopram (90 g, 0.28 mol) containing desmethyl citalopram (7 %, HPLC), formic acid (98%, 2.7 g) was added followed by aqueous formaldehyde(35%, 2.37 g). The reaction mass was heated at 85-95° for 30 min, cooled to 30°, and diluted with ethanol (900 mL), treated with oxalic acid dihydrate (41.94 g, 0.33 mol), and heated to reflux. The obtained solution was cooled to 20-25° and stirring was continued for 2 h at 20-25°, followed by collecting the product by filtration and recrystn. from ethanol to give highly pure 92 g crystalline citalopram oxalate having HPLC purity 99.7% wherein desmethyl citalopram (impurity) was not detected.

IT **64169-39-7**, 5-Bromo-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of pure citalopram by N-methylation of crude citalopram containing desmethyl citalopram with formaldehyde and formic acid)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



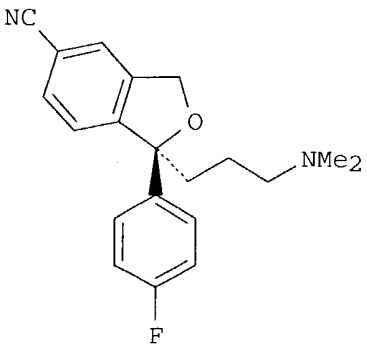
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:633919 CAPLUS
DOCUMENT NUMBER: 141:157024
TITLE: A processes for preparation of escitalopram, useful as antidepressant
INVENTOR(S): Nannapaneni, Venkaiah Chowdary; Muddasani, Pulla Reddy; Talasila, Sambashiva Rao; Nekkanti, Srinivasa Rao; Podile, Khadgapathi
PATENT ASSIGNEE(S): Natco Pharma Limited, India
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

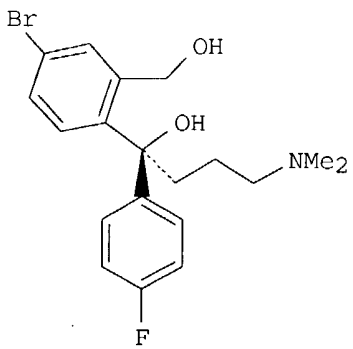
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004065375	A1	20040805	WO 2003-IN220	20030617

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IN 2003-MA52 A 20030117
GI



I



II

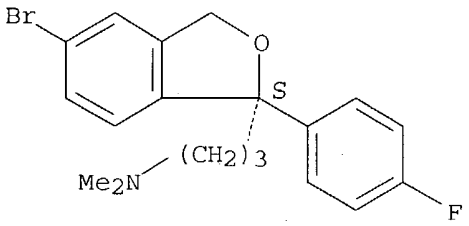
AB The present invention relates to an improved process for the preparation of escitalopram (I) which consist of a sequential double Grignard reaction on 5-bromophthalide, isolation of di-magnesium salt, neutralization of di-magnesium salt, resolution of dihydroxy compound of the formula II, cyclization, and cyanation. The proposed process utilizes the insol. property of di-magnesium salt in a mixture of THF and a non-polar organic solvent, and separates it from impurities by simple filtration thereby making the isolation and purification process simple. Advantages of the proposed process include (a) high yield preparation of escitalopram (>25%), (b) escitalopram can be prepared in a simple and easy to adopt manner without involving any purification steps, (c) the process produces pure (>98%) di-magnesium salt of intermediate compound was isolated, etc.

IT **488148-14-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(processes for the preparation of escitalopram and its precursor)

RN 488148-14-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:331827 CAPLUS

DOCUMENT NUMBER: 140:357194

TITLE: Process for the manufacture of citalopram hydrobromide from 5-bromophthalide

INVENTOR(S): Chodankar, Nandkumar; Bhobe, Ajit; Oak, G. M.; Eappan, Philip

PATENT ASSIGNEE(S): Sekhsaria Chemicals Limited, India

SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004077870	A1	20040422	US 2002-277451	20021022
PRIORITY APPLN. INFO.:			US 2002-277451	20021022

OTHER SOURCE(S): CASREACT 140:357194; MARPAT 140:357194

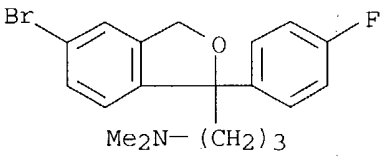
AB Disclosed is a process for the preparation of 1-(4-fluorophenyl)-1-(3-dimethylamino-propyl)-5-phthalanecarbonitrile (citalopram) (known antidepressant) or a pharmaceutically acceptable salt thereof, comprising performing two successive Grignard reactions on 5-bromophthalide using p-fluorobromobenzene and then N,N-dimethylaminopropylmagnesium chloride, wherein the 5-bromophthalide is reacted with the first Grignard reagent in

the presence of a Lewis acid, so reducing byproduct formation and improving yields.

IT **64169-39-7P**, 1-(4-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(manufacture of citalopram hydrobromide from 5-bromophthalide by two successive Grignard reactions on 5-bromophthalide using p-fluorobromobenzene and then N,N-dimethylaminopropylmagnesium chloride)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:101152 CAPLUS

DOCUMENT NUMBER: 140:145992

TITLE: Process for the preparation of 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile

INVENTOR(S): Hilden, Leif; Rummakko, Petteri; Grumann, Arne; Pietikaeinen, Pekka

PATENT ASSIGNEE(S): Orion Corporation Fermion, Finland

SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004011450	A1	20040205	WO 2003-FI557	20030710

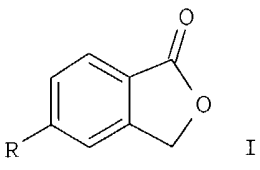
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

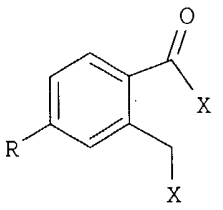
PRIORITY APPLN. INFO.: FI 2002-1421 A 20020730

OTHER SOURCE(S): CASREACT 140:145992; MARPAT 140:145992

GI



I



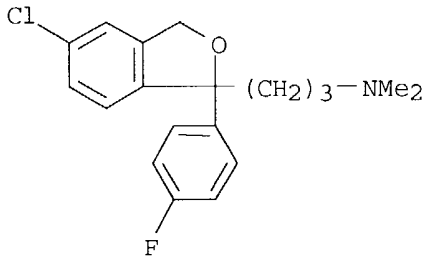
II

AB The present invention is directed to novel processes for the preparation of citalopram comprising halogenation of a phthalides I (wherein R is a suitable group to be changed to CN) to afford an acid halides II (X is halogen) and thereafter obtaining citalopram through two successive reactions with suitable organometallic halides or organoboranes or by a reaction with organometallic 4-fluorophenylhalide or 4-fluorophenylborane followed by reduction and alkylation, and an exchange of R to cyano to afford citalopram. The order of the reactions can be varied depending e.g. on the starting compound used.

IT **64169-45-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of citalopram)

RN 64169-45-5 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:837069 CAPLUS

DOCUMENT NUMBER: 139:337880

TITLE: Preparation of escitalopram via the chiral enriched diol monoesters of (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol

INVENTOR(S): Tse, Hoi Lun Allan

PATENT ASSIGNEE(S): Torcan Chemical Ltd., Can.

SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003087081	A1	20031023	WO 2003-CA522	20030408

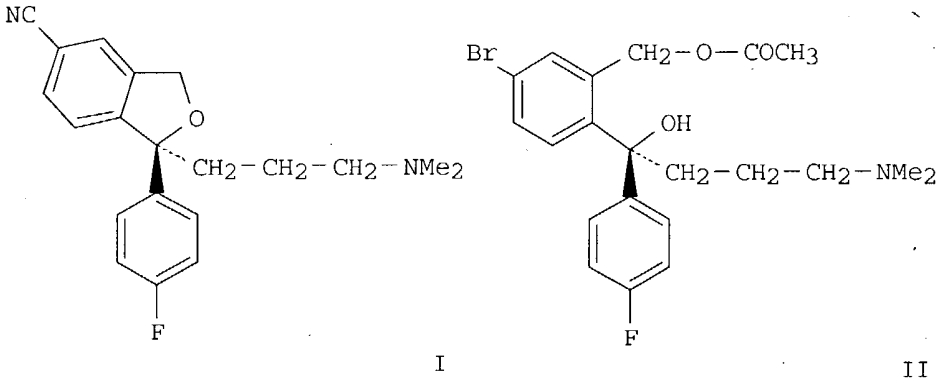
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: CA 2002-2381341 A 20020409
OTHER SOURCE(S): CASREACT 139:337880

GI



I II

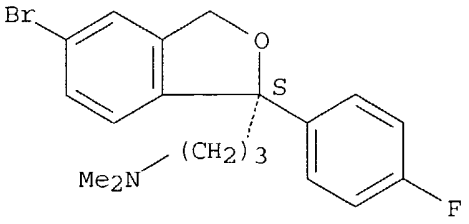
AB Preparation of escitalopram (I) via the chiral enriched monoacetate ester of (4-bromo-2-(hydroxymethyl)phenyl)-(4-fluorophenyl)methanol (II) was disclosed. For example, a racemic mixture of monoacetate ester II (13.52 g) and (+)-di-p-toluoyl tartaric acid (11.92 g) in acetone (135 mL) was heated at reflux until a pale brown solution was obtained. The solution was cooled, the acetone removed under vacuum and the resulting brown foam recrystd. from acetone-hexane (2:1) to afford the (+)-di-p-toluoyl tartaric acid salt of monoacetate ester II with a diastereomeric ratio of 97:3. Of note, the claimed (+)-di-p-toluoyl tartaric acid salt of monoacetate ester II was converted to escitalopram oxalate in 4-steps with [α]D = +10.1° (at 20°C, c 0.95 in MeOH).

IT **488148-14-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of escitalopram via a chiral enriched diol monoester intermediate)

RN 488148-14-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, (1S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:590880 CAPLUS
DOCUMENT NUMBER: 139:133459
TITLE: Cyanation process for the preparation of citalopram and its extractive purification
INVENTOR(S): Coppi, Laura; Gasanz Guillen, Yolanda; Campon Pardo, Julio
PATENT ASSIGNEE(S): Esteve Quimica, S.A., Spain
SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003144534	A1	20030731	US 2003-351289	20030124
US 6635773	B2	20031021		
ES 2194597	A1	20031116	ES 2002-167	20020125
WO 2003062218	A1	20030731	WO 2003-ES37	20030124

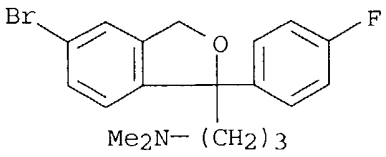
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: ES 2002-167 A 20020125

AB Crude citalopram was prepared the cyanation of 1-[3-(dimethylamine)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-bromoisobenzofuran with copper cyanide and purified citalopram or one of its salts (e.g., citalopram hydrobromide) was obtained by the extractive purification of citalopram by selective extns. of citalopram or it salts of its impurities with organic solvents (e.g., toluene and heptane) and water under specific conditions of pH and temperature

IT **64169-39-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyanation process for the preparation of citalopram and its extractive purification)

RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)

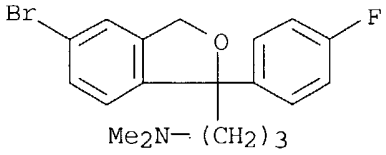


L10 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:563665 CAPLUS
DOCUMENT NUMBER: 140:38042
TITLE: Synthesis and biological evaluation of novel carbon-11-labelled analogues of citalopram as potential radioligands for the serotonin transporter
AUTHOR(S): Madsen, Jacob; Merachtsaki, Pinelopi; Davoodpour, Padideh; Bergstrom, Mats; Langstrom, Bengt; Andersen, Kim; Thomsen, Christian; Martiny, Lars; Knudsen, Gitte M.
CORPORATE SOURCE: PET & Cyclotron Unit 3982, Copenhagen University Hospital, Copenhagen, 2100, Den.
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(16), 3447-3456
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Three serotonin reuptake inhibitors where the 5-cyano group in citalopram [1-(3-dimethylamino-propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (1)] was replaced with a Me, acetyl and piperidinyl carbonyl group, resp., were synthesized. In a Stille reaction applying [11C]methyl iodide the labeled compound [5-methyl-11C]{3-[1-(4-fluorophenyl)-5-methyl-1,3-dihydroisobenzofuran-1-yl]-propyl}-dimethylamine ([11C]-2) was synthesized in 60-90% radiochem. yield. [5-carbonyl-11C]{1-[1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-yl]-1-piperidin-1-yl-methanone} ([11C]-3) was synthesized in 62% radiochem. yield in a palladium mediated cross-coupling reaction utilizing [11C]carbon monoxide. The specific activity of [11C]-2 was highly dependent on whether the corresponding trimethyltin or tributyltin precursor was applied. In ex vivo rodent studies compound [11C]-2 exhibited a good blood-brain barrier (BBB) penetration whereas [11C]-3 did not. The brain distribution of [11C]-2 was investigated in a non-human primate using PET. There was a rapid uptake of radioactivity into the brain. Accumulation of the radiotracer was in agreement with the known distribution of serotonin transporters. The maximal thalamus to cerebellum ratio of 1.3 was reached after 85 min and the specific binding was partly blocked after pre-treatment with citalopram. Thus, [11C]-2 does not exhibit appropriate properties as radioligand for visualization of the serotonin transporter in vivo.

IT **64169-39-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(11C-labeled analogs of citalopram as potential radioligands for serotonin transporter)

RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:551309 CAPLUS
DOCUMENT NUMBER: 139:117333
TITLE: Process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile via cyanation of the corresponding chloride or bromide precursors.
INVENTOR(S): Thennati, Rajamannar; Kilaru, Srinivasu; Chinnapillai, Rajendran; Patel, Nileshkumar Sureshbhai
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

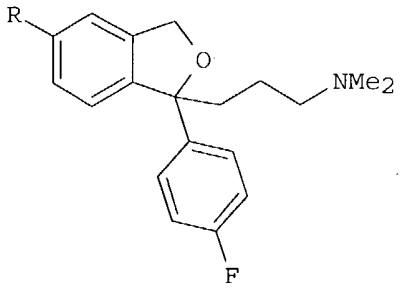
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057132	A2	20030717	WO 2003-IN6	20030107
WO 2003057132	A3	20040226		
WO 2003057132	C1	20040415		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
IN 2002-MU10 A 20020107
IN 2002-MU18 A 20020110
IN 2002-MU847 A 20020930

OTHER SOURCE(S): CASREACT 139:117333; MARPAT 139:117333
GI



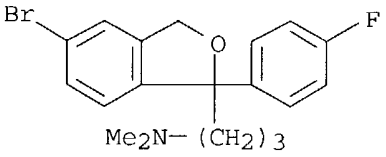
I

AB Title compound (I; R = cyano) (citalopram) was prepared by treatment of I (R = Cl, Br) with a cyanide source in the presence of I- in an amide, amine, or polyether solvent followed by treatment of the crude product containing 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile and 5-carboxamido-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)phthalide impurities with a phosphorus oxyhalide, phosphorus oxide cyanide reversal agent, and purification using a solvent system comprising a hydrocarbon and alc., ester, ether, ketone, or mixture thereof. Thus, citalopram containing 4.7% amide and 0.72% desmethylcitalopram impurities was heated with POCl3 in PhMe at 70° for 1 h. The mixture was poured into water and pH was adjusted to 2.0-2.5 with aqueous HCl. The PhMe layer was separated and the pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous NH3 followed by extraction with PhMe to give product containing 0.05% and 0.23% of the amide and desmethylcitalopram resp.

IT **64169-39-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of citalopram via cyanation of the corresponding chloride or bromide precursor)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:282554 CAPLUS

DOCUMENT NUMBER: 138:305791

TITLE: Process for the preparation of citalopram, and intermediates and derivatives

INVENTOR(S): Malik, A. Aslam; Palandoken, Hasan; Stringer, Joy A.; Huang, Dershing; Romero, Antonio; Dapremont, Olivier

PATENT ASSIGNEE(S): Pharmachem Technologies Limited, UK

SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029236	A1	20030410	WO 2002-EP10645	20020923
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003153774	A1	20030814	US 2002-242322	20020911
EP 1430044	A1	20040623	EP 2002-779403	20020923
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			US 2001-324821P	P 20010924
			US 2002-242322	A 20020911
			WO 2002-EP10645	W 20020923

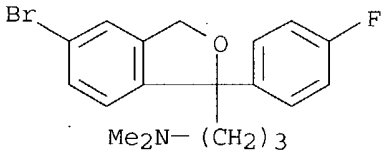
OTHER SOURCE(S): CASREACT 138:305791

AB The present invention provides a process for the preparation of Citalopram, a known antidepressant.

IT **64169-39-7P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(process for the preparation of citalopram and derivs.)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:172971 CAPLUS

DOCUMENT NUMBER: 138:221462

TITLE: Improved process for the manufacture of citalopram hydrobromide from 5-bromophthalide

PATENT ASSIGNEE(S): Sekhsaria Chemicals Ltd., India

SOURCE: Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

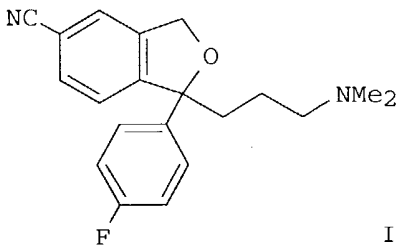
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1288211	A1	20030305	EP 2002-255750	20020819
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			US 2001-315391P	P 20010828

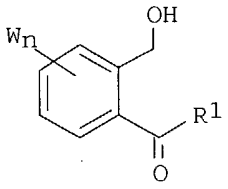
10/750,049

OTHER SOURCE(S): CASREACT 138:221462; MARPAT 138:221462

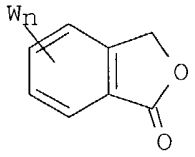
GI



I



II



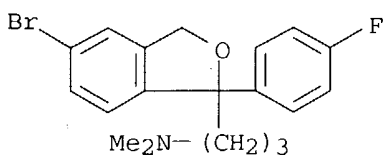
III

AB A process for the preparation of 1-(4'-fluorophenyl)-1-(3-dimethylamino-propyl)-5-phthalanecarbonitrile (I), or a pharmaceutically acceptable salt thereof, comprising performing two successive Grignard reactions on 5-bromophthalide, wherein the 5-bromophthalide is reacted with the first Grignard reagent in the presence of a Lewis acid, so reducing byproduct formation and improving yields. Also claimed is a process for the preparation of aryl ketone II [R1 = (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aralkyl, optionally containing one heteroatom; W = haloge, CN, OH, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aralkyl; n = 0 - 4] which comprises the step of reacting a phthalide III with a Grignard reagent, R1MgY (Y = halogen) and is characetrized in that the phthalide is reacted with a Lewis acid to form an adduct prior to reaction with the Grignard reagent. Thus,.

IT **64169-39-7P**, 1-(4-Fluorophenyl)-1-(3-dimethylamino-propyl)-5-bromophthalane
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyanation of; improved process for the manufacture of citalopram
hydrobromide from 5-bromophthalide)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



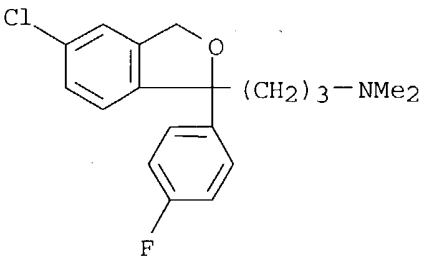
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:83756 CAPLUS
DOCUMENT NUMBER: 139:332852
TITLE: Effects of acute and chronic administration of selective monoamine re-uptake inhibitors in the rat forced swim test
AUTHOR(S): Kelliher, P.; Kelly, J. P.; Leonard, B. E.; Sanchez, C.
CORPORATE SOURCE: Dept. of Pharmacology, Natl. Univ. of Ireland, Galaway, Ire.
SOURCE: Psychoneuroendocrinology (2003), 28(3), 332-347
CODEN: PSYCDE; ISSN: 0306-4530
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The rat forced swim test (FST) is a model that is used extensively as a screening test for antidepressant activity. It has previously been reported that thorough anal. of behavior in this model reveals two distinct types of active response - climbing and swimming - and that these are sep. evoked by re-uptake inhibitors selective for noradrenaline (NA) and serotonin (5-HT), resp. In the present study, utilizing re-uptake inhibitors selective for NA, talsupram, and 5-HT, 5-chloro-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)- phthalan (Lu 10-134-C), we examined if this scoring technique could detect the antidepressant potential of a selective serotonin re-uptake inhibitor (SSRI), and whether re-uptake inhibitors selective for distinct monoamine systems induce exclusive behavioral responses. We also analyzed if chronic antidepressant administration for three weeks was more effective than acute treatment. We found Lu 10-134-C (40 mg/kg; PO) to be behaviorally active in this paradigm. Although treatment with talsupram (40 mg/kg; PO) resulted solely in climbing behavior, Lu 10-134-C induced both climbing and swimming behavior. However, chronic pre-treatment with either re-uptake inhibitor (20 mg/kg; twice daily; PO) failed to augment the response observed with acute treatment. Similarly, chronic administration of either compound was without effect on the basal, or stress-induced, serum corticosterone concns. or anterior pituitary (AP) preproopiomelanocorticotropin (POMC) mRNA expression. These results suggest that selective monoamine re-uptake inhibition produces distinct, but not necessarily exclusive, behavioral responses in the forced swim test.

IT **64169-45-5**, Lu 10-134C
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidepressant potential of selective monoamine re-uptake inhibitors in rat forced swim test)

RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:58074 CAPLUS
DOCUMENT NUMBER: 138:122548
TITLE: Method for the preparation of escitalopram via chromatographic resolution of citalopram or its intermediates using carbohydrate-based chiral stationary phases
INVENTOR(S): Bech Sommer, Michael; Nielsen, Ole; Petersen, Hans; Ahmadian, Haleh; Pedersen, Henrik; Brosen, Peter; Geiser, Fiona; Lee, James; Cox, Geoffey; Dapremont, Olivier; Suteu, Christina; Assenza, Sebastian P.; Hariharan, Shankar; Nair, Usha
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

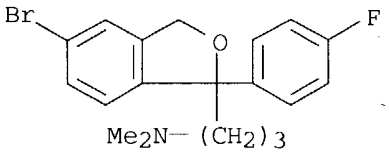
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006449	A1	20030123	WO 2002-DK491	20020712
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1409472	A1	20040421	EP 2002-750836	20020712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002010817	A	20040622	BR 2002-10817	20020712
PRIORITY APPLN. INFO.:			DK 2001-1101 A	20010713
			DK 2001-1851 A	20011211
			DK 2001-1852 A	20011211
			WO 2002-DK491 W	20020712

OTHER SOURCE(S): CASREACT 138:122548
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A novel method is provided for the manufacture of the antidepressant escitalopram, i.e., (S)-I. The method comprises chromatog. separation of the enantiomers of either (1) citalopram, i.e., (±)-I, or (2) an intermediate in its production, using a chiral stationary phase such as Chiralpak® AD or Chiralcel® OD. Novel chiral intermediates for the synthesis of escitalopram, made by said method, are also provided. For example, the intermediate nitrile diol (±)-II was resolved using Chiralpak® AD stationary phase on a Novasep Licosep® 10-50

phases)
RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)

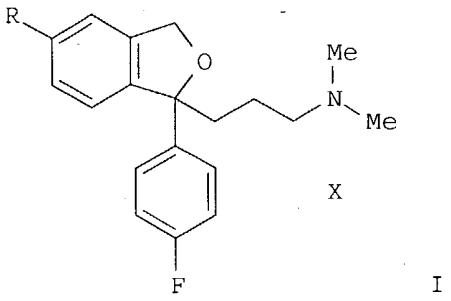


REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:32670 CAPLUS
DOCUMENT NUMBER: 138:55856
TITLE: Process for the preparation of highly pure salts of citalopram
INVENTOR(S): Satyanarayana, Chava; Venkata, Ramana Rao Chunchu; Jyothi, Basu Abbineni; Hari, Babu Bobepudi
PATENT ASSIGNEE(S): Matrix Laboratories Limited, India
SOURCE: Brit. UK Pat. Appl., 18 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2375763	A1	20021127	GB 2002-10225	20020503
GB 2375763	B2	20030924		
WO 2003072565	A1	20030904	WO 2002-IB3832	20020418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2002009194	A	20040608	BR 2002-9194	20020418
GB 2387596	A1	20031022	GB 2003-15853	20020503
GB 2387596	B2	20040211		
GB 2387844	A1	20031029	GB 2003-15852	20020503
PRIORITY APPLN. INFO.:			GB 2002-4607 A	20020227
			WO 2002-IB3832 W	20020418
			GB 2002-10225 A	20020503

GI

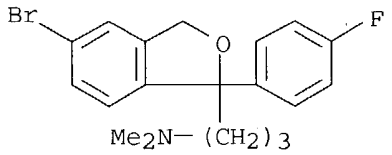


I

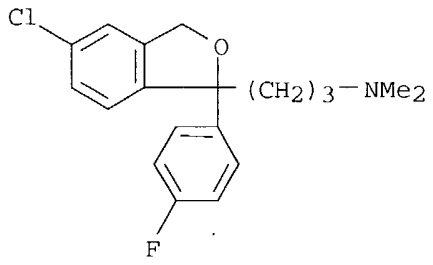
AB A process for preparing highly pure salts of citalopram, such as I (R = CN; X = oxalate, hydrobromide, hydrochloride), for pharmaceutical compns. was described. Thus, citalopram contaminated with up to 5.0% of desmethyl citalopram was added to acetone and stirred for 15 min at 40° followed by addn of oxalic acid to form citalopram oxalate in 85% yield with desmethyl citalopram content <0.1%.

IT **64169-39-7 64169-45-5**
RL: REM (Removal or disposal); PROC (Process)
(process for the preparation of highly pure salts of citalopram)

RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



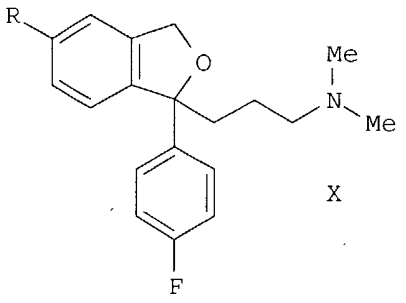
L10 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:8116 CAPLUS
DOCUMENT NUMBER: 138:55857
TITLE: Process for the preparation of citalopram
INVENTOR(S): Hamied, Yusuf Khwaja; Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India
SOURCE: Brit. UK Pat. Appl., 11 pp.
CODEN: BAXXDU

10/750,049

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2376945	A1	20021231	GB 2001-15708	20010627
PRIORITY APPLN. INFO.:			GB 2001-15708	20010627

OTHER SOURCE(S): CASREACT 138:55857; MARPAT 138:55857
GI



I

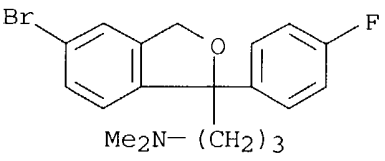
AB An improved process for the preparation of citalopram via substitution of the halogen of halophthalane salts I (R = halogen; X = oxalate, fumarate, maleate, citrate, acetate, formate, hydrochloride, hydrobromide, sulfate) using cuprous cyanide in an organic solvent. Thus, bromophthalane oxalate I (R = Br, X = oxalate) was reacted CuCN in diglyme under a nitrogen atmospheric at 150-155° for 3 h to form citalopram which was converted to its HBr salt I (R = CN, X = HBr).

IT **64372-43-6 479065-02-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of citalopram)

RN 64372-43-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

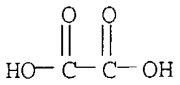
CM 1

CRN 64169-39-7
CMF C19 H21 Br F N O

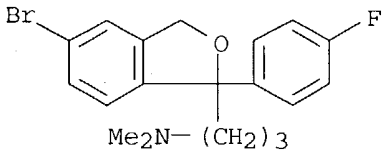


CM 2

CRN 144-62-7
CMF C2 H2 O4



RN 479065-02-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrobromide (9CI) (CA INDEX NAME)



● HBr

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:716262 CAPLUS
DOCUMENT NUMBER: 137:232543
TITLE: Cyanation process for the preparation of citalopram
INVENTOR(S): Biswas, Sujay; Sharma, Tarun Kant; Kumar, Yatendra; Sathyanarayana, Swargam; Vijayaraghavan, Bakthavathsalan
PATENT ASSIGNEE(S): Ranbaxy Laboratories Limited, India
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072565	A1	20020919	WO 2002-IB690	20020308
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1370545	A1	20031217	EP 2002-702634	20020308
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: IN 2001-DE264 A 20010309
WO 2002-IB690 W 20020308

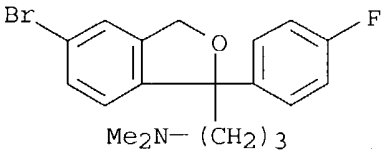
OTHER SOURCE(S): CASREACT 137:232543

AB An improved and industrially advantageous process for the preparation of citalopram and pharmaceutically acceptable acid addition salts consists of reacting a precursor substituted with a bromo or an iodo group in the same

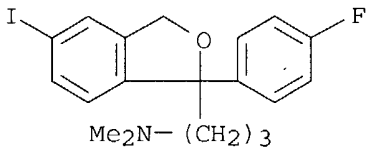
position as the cyano group in citalopram with a cyanide source in a solvent in the present of a N-containing base; the **citalopram free base** may then be salified with a pharmaceutically acceptable acids.

IT **64169-39-7 260066-78-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyanation process for the preparation of citalopram from)

RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 260066-78-2 CAPLUS
CN 1-Isobenzofuranpropanamine, 1-(4-fluorophenyl)-1,3-dihydro-5-iodo-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:695968 CAPLUS
DOCUMENT NUMBER: 137:216863
TITLE: Preparation of phthalanes
INVENTOR(S): Hamied, Yusuf Khwaja; Kankan, Rajendra Narayanrao; Rao, Dhanmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Ltd., India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 11 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

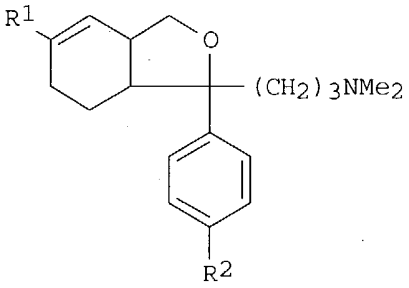
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070501	A1	20020912	WO 2002-GB1054	20020307
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1366034	A1	20031203	EP 2002-702553	20020307

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

EE 200300424	A	20031215	EE 2003-424		20020307
US 2004092755	A1	20040513	US 2003-471052		20031118
PRIORITY APPLN. INFO.:			GB 2001-5627	A	20010307
			WO 2002-GB1054	W	20020307

OTHER SOURCE(S): CASREACT 137:216863; MARPAT 137:216863

GI



I

AB Citalopram and other phthalanes I [R1 = CN, R2 = halogen, trifluoromethyl, CN, acyl] are made by treating a salt of I [R1 = halogen] with cuprous cyanide. Thus, 100g I.oxalate [R1 = Br, R2 = F] was treated with 35 g CuCN in diglyme at 150-155° for 3 h to give 35 g I [R1 = CN, R2 = F] as the hydrobromide.

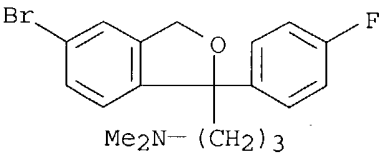
IT **64372-43-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of phthalanes)

RN 64372-43-6 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

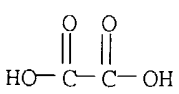
CM 1

CRN 64169-39-7
CMF C19 H21 Br F N O



CM 2

CRN 144-62-7
CMF C2 H2 O4



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:550142 CAPLUS
DOCUMENT NUMBER: 137:78853
TITLE: Preparation of Citalopram from 5-halo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran.
INVENTOR(S): Petersen, Hans; Ahmadian, Haleh
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: Patentschrift (Switz.), 15 pp.
CODEN: SWXXAS
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CH 691969	A	20011215	CH 2001-1522	20010816
FI 2001001621	A	20020219	FI 2001-1621	20010809
FI 2001001622	A	20020219	FI 2001-1622	20010809
CA 2354880	C	20030603	CA 2001-2354880	20010809
IT 2001MI1785	A1	20020218	IT 2001-MI1785	20010813
IT 2001MI1786	A1	20020218	IT 2001-MI1786	20010813
GB 2362647	A1	20011128	GB 2001-19733	20010814
GB 2362647	B2	20020918		
ZA 2001006687	A	20020214	ZA 2001-6687	20010814
DK 200101216	A5	20020219	DK 2001-1216	20010814
DK 200101219	A5	20020219	DK 2001-1219	20010814
NO 2001003942	A	20020219	NO 2001-3942	20010814
NO 2001003943	A	20020219	NO 2001-3943	20010814
GB 2365865	A1	20020227	GB 2001-19734	20010814
GB 2365865	B2	20020717		
US 2002025982	A1	20020228	US 2001-930107	20010814
US 6426422	B2	20020730		
US 2002026062	A1	20020228	US 2001-930110	20010814
US 6509483	B2	20030121		
WO 2002016341	A1	20020228	WO 2001-DK541	20010814
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2002016342	A1	20020228	WO 2001-DK542	20010814
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001079608	A5	20020304	AU 2001-79608	20010814

AU 2001079609	A5	20020304	AU 2001-79609		20010814
GR 2001100397	A	20020524	GR 2001-100397		20010814
GR 1004635	B2	20040714			
ZA 2001006683	A	20020805	ZA 2001-6683		20010814
GR 1004074	B2	20021126	GR 2001-100398		20010814
GR 2001100398	A	20020524			
EP 1309581	A1	20030514	EP 2001-957785		20010814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
EP 1309582	A1	20030514	EP 2001-957786		20010814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004506729	T2	20040304	JP 2002-521442		20010814
JP 2004506730	T2	20040304	JP 2002-521443		20010814
NZ 523853	A	20040730	NZ 2001-523853		20010814
NZ 523877	A	20040827	NZ 2001-523877		20010814
NL 1018775	C1	20011024	NL 2001-1018775		20010816
NL 1018776	C1	20011024	NL 2001-1018776		20010816
BE 1013443	A6	20020115	BE 2001-548		20010816
FR 2813077	A1	20020222	FR 2001-10855		20010816
FR 2813077	B1	20040820			
FR 2813078	A1	20020222	FR 2001-10857		20010816
FR 2813078	B1	20040402			
DE 10140028	A1	20020418	DE 2001-10140028		20010816
DE 10140029	A1	20020502	DE 2001-10140029		20010816
CN 1339435	A	20020313	CN 2001-133947		20010817
CN 1339436	A	20020313	CN 2001-133948		20010817
BR 2001004841	A	20020604	BR 2001-4841		20010817
ES 2170734	A1	20020801	ES 2001-1919		20010817
ES 2170735	A1	20020801	ES 2001-1920		20010817
BE 1013444	A6	20020115	BE 2001-550		20010820
BR 2001005022	A	20020604	BR 2001-5022		20010824
BG 107583	A	20040130	BG 2003-107583		20030224
BG 107584	A	20040130	BG 2003-107584		20030224
PRIORITY APPLN. INFO.:			DK 2000-1231	A	20000818
			WO 2001-DK541	W	20010814
			WO 2001-DK542	W	20010814

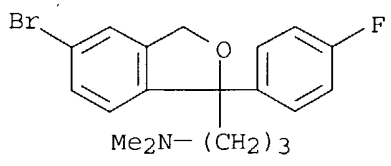
OTHER SOURCE(S): CASREACT 137:78853

AB Citalopram (I) was prepared by converting a 5-halo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran to the 5-carboxylic acid derivative and converting the latter to I. Thus, 5-bromo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran in Me3COMe at -78° was treated with BuLi followed by stirring for 2 h at -30°. Solid CO2 was added followed by stirring for 16 h at room temperature to give 5-carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran. The latter was heated with sulfamide and SOCl2 in sulfolane at 130° for 2 h to give I.

IT **64169-39-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Citalopram from 5-halo-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran)

RN 64169-39-7 CAPLUS

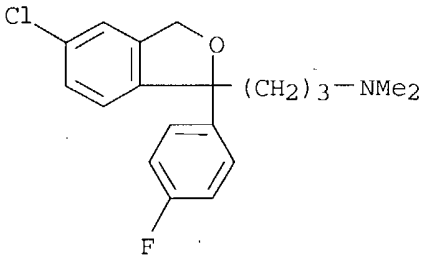
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:790502 CAPLUS
DOCUMENT NUMBER: 136:112549
TITLE: Species-scanning mutagenesis of the serotonin transporter reveals residues essential in selective, high-affinity recognition of antidepressants
AUTHOR(S): Mortensen, Ole V.; Kristensen, Anders S.; Wiborg, Ove
CORPORATE SOURCE: Laboratory of Molecular Neurobiology, Department of Biological Psychiatry, Psychiatric University Hospital, Risskov, 8240, Den.
SOURCE: Journal of Neurochemistry (2001), 79(2), 237-247
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The serotonin transporter (SERT) is a high-affinity sodium/chloride-dependent neurotransmitter transporter responsible for reuptake of serotonin from the extracellular space. SERT is a selective target of several clin. important antidepressants. In a cross-species anal. comparing human and bovine SERTs, the kinetic parameters for serotonin uptake were found to be similar, however, the pharmacol. profiles of the two transporters differ. Following transient expression in COS-1 cells, IC50 values were determined for several antidepressants and psychostimulants. The potencies of the antidepressants citalopram, fluoxetine, paroxetine and imipramine were several-fold higher at hSERT compared with bSERT. No species selectivity was observed for the antidepressants fluvoxamine, and sertraline or for the psychostimulants cocaine, the cocaine analog β-carbomethoxy-3β-(4-iodophenyl)tropane, or for 3,4-methylenedioxymethamphetamine (MDMA). Anal. of six hSERT/bSERT chimeras and subsequent species-scanning mutagenesis of each isoform revealed methionine-180, tyrosine-495, and phenylalanine-513 to be responsible for the increase in citalopram and paroxetine potencies at hSERT and methionine-180 and phenylalanine-513 to confer species selectivity at hSERT for fluoxetine and imipramine. Results were obtained by doing the forward, bovine to human, mutations and confirmed by doing the reverse mutations. Citalopram analogs were used to define the roles of methionine-180, tyrosine-495, and phenylalanine-513 and to reveal mol. interactions with individual functional groups of citalopram. We suggest that methionine-180 interacts with the heterocyclic nucleus of citalopram or stabilizes the binding pocket and phenylalanine-513 to be a steric blocker of antidepressant recognition.

IT **64169-45-5**, LU10-134C
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(species-scanning mutagenesis of serotonin transporter reveals residues essential in selective, high-affinity recognition of antidepressants)
RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

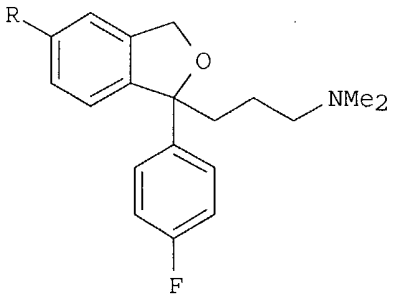
L10 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:592319 CAPLUS
Correction of: 2001:386023
DOCUMENT NUMBER: 135:137393
Correction of: 134:353251
TITLE: Method for the preparation of citalopram
INVENTOR(S): Petersen, Hans; Rock, Michael Harold
PATENT ASSIGNEE(S): H Lundbeck A/S, Den.
SOURCE: Brit. UK Pat. Appl., 15 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2354240	A1	20010321	GB 2001-1508	19991119
GB 2354240	B2	20010523		
IT 99MI1579	A1	20010115	IT 1999-MI1579	19990715
WO 2000011926	A2	20000309	WO 1999-DK643	19991119
WO 2000011926	A3	20000629		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1105382	A2	20010613	EP 1999-968206	19991119
EP 1105382	B1	20020213		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
DE 19983486	T	20011018	DE 1999-19983486	19991119
DE 19983486	C2	20020905		
AT 213237	E	20020215	AT 1999-968206	19991119
BR 9917367	A	20020305	BR 1999-17367	19991119
AT 9909040	A	20020515	AT 1999-9040	19991119
AT 409960	B	20021227		
TR 200103700	T2	20020521	TR 2001-200103700	19991119
JP 2002523432	T2	20020730	JP 2000-567065	19991119
JP 3389571	B2	20030324		
PT 1105382	T	20020731	PT 1999-968206	19991119
ES 2172356	T3	20020916	ES 1999-968206	19991119
CZ 292174	B6	20030813	CZ 2001-319	19991119

CN 1129593	B	20031203	CN 1999-816768		19991119
NZ 514982	A	20040130	NZ 1999-514982		19991119
CA 2290125	C	20040810	CA 1999-2290125		19991122
NO 2001000318	A	20010220	NO 2001-318		20010119
SE 2001000194	A	20010425	SE 2001-194		20010124
SE 516689	C2	20020212			
FI 2001000154	A	20010209	FI 2001-154		20010125
ZA 2001007956	A	20020927	ZA 2001-7956		20010927
ZA 2001008855	A	20020611	ZA 2001-8855		20011026
US 2002061925	A1	20020523	US 2001-12025		20011106
US 6750358	B2	20040615			
BG 106190	A	20020830	BG 2001-106190		20011207
ZA 2002005023	A	20030623	ZA 2002-5023		20020621
PRIORITY APPLN. INFO.:			DK 1999-921	A	19990625
			WO 1999-DK643	W	19991119

OTHER SOURCE(S): CASREACT 135:137393; MARPAT 135:137393

GI



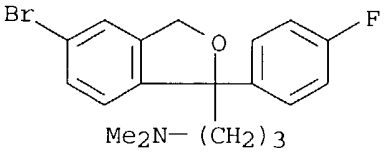
I

AB A method for preparing the antidepressant, citalopram [I; R = CN], by reacting an isobenzofuranpropanamine [I; R = Cl or Br] with a cyanide source in the presence of a nickel catalyst is presented. Citalopram is produced in high yield as a very pure product using this catalytic process. Thus, sequential addition of I (R = Cl) and NaCN to the Ni catalyst formed by reflux of NiCl2 with PPh3 in AcCN in the presence of a catalytic amount of Zn, followed by workup and treatment with oxalic acid, gave citalopram oxalate in 55% yield.

IT **64169-39-7**, 1-(4-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane **64169-45-5**, 1-(4-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of citalopram by nickel-catalyzed cyanation of halo precursors)

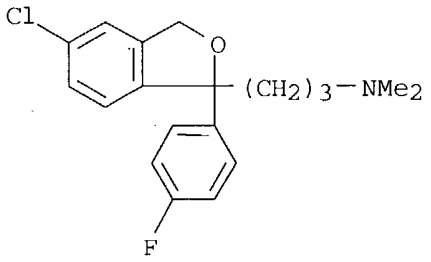
RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 64169-45-5 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



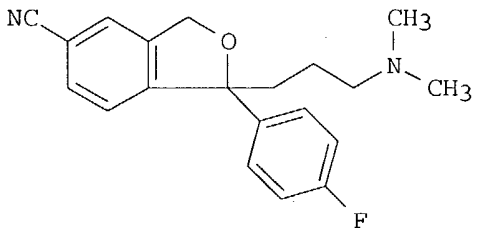
L10 ANSWER 20 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:489362 CAPLUS
DOCUMENT NUMBER: 135:61225
TITLE: Process for the preparation of high-purity citalopram by cyanidation with purification via thin-film distillation
INVENTOR(S): Castellin, Andrea; Volpe, Giulio; Sbrogio, Federico
PATENT ASSIGNEE(S): H. Lundbeck A/s, Den.
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047877	A2	20010705	WO 2001-DK148	20010307
WO 2001047877	A3	20001227		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2359810	AA	20010705	CA 2001-2359810	20010307
CA 2359810	C	20021105		
AU 2001039202	A5	20010709	AU 2001-39202	20010307
EP 1181272	A2	20020227	EP 2001-913727	20010307
EP 1181272	B1	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2001006271	A	20020521	BR 2001-6271	20010307
TR 200200018	T1	20020621	TR 2002-200200018	20010307
AT 222899	E	20020915	AT 2001-913727	20010307
PT 1181272	T	20030131	PT 2001-913727	20010307
ES 2181663	T3	20030301	ES 2001-1913727	20010307
JP 2003519121	T2	20030617	JP 2001-549350	20010307
NL 1017534	C1	20010426	NL 2001-1017534	20010308
DK 200100386	A5	20020629	DK 2001-386	20010308
GB 2356199	A1	20010516	GB 2001-5981	20010312
GB 2356199	B2	20011003		
CZ 293140	B6	20040218	CZ 2001-891	20010312
NO 2001001272	A	20020701	NO 2001-1272	20010313

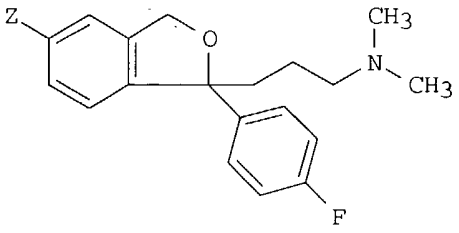
GR 2001100131	A	20021009	GR 2001-100131		20010316
DE 10112828	C1	20021121	DE 2001-10112828		20010316
DE 10164725	A1	20030206	DE 2001-10164725		20010316
DE 10164725	B4	20040826			
CH 691536	A	20010815	CH 2001-546		20010322
BE 1013417	A6	20011204	BE 2001-189		20010322
FR 2818977	A1	20020705	FR 2001-4025		20010326
FR 2818977	B1	20031205			
NL 1018410	C1	20011113	NL 2001-1018410		20010628
BE 1013316	A6	20011106	BE 2001-466		20010709
GB 2361697	A1	20011031	GB 2001-17095		20010713
CH 691999	A	20010726	CH 2001-1412		20010726
ES 2170733	A1	20020801	ES 2001-1763		20010727
ES 2170733	B1	20031216			
AU 750006	B1	20020711	AU 2001-65478		20010827
SE 2001003044	A	20020629	SE 2001-3044		20010914
ZA 2001010133	A	20030113	ZA 2001-10133		20011210
BG 106219	A	20020830	BG 2001-106219		20011213
US 2002087012	A1	20020704	US 2001-35005		20011220
NZ 516299	A	20021220	NZ 2001-516299		20011220
HR 2002000005	A1	20030430	HR 2002-5		20020104
US 2003178295	A1	20030925	US 2003-361800		20030210
PRIORITY APPLN. INFO.:			DK 2000-1943	A	20001228
			WO 2001-DK148	W	20010307
			NL 2001-1017534	A	20010308
			CH 2001-546	A	20010322
			US 2001-35005	A1	20011220

OTHER SOURCE(S): CASREACT 135:61225; MARPAT 135:61225

GI



I



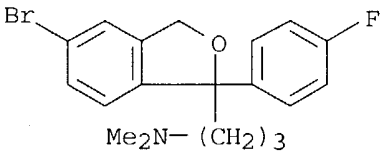
II

AB High-purity citalopram (I) is prepared on an industrial scale by: subjecting a citalopram precursor [II; Z = iodo, bromo, chloro, CF3(CF2)nSO2O; n = 0-8] (e.g., Z = Br) to a cyanide exchange reaction in which the group Z is exchanged with cyanide by reaction with a cyanide source (e.g., CuCN) in a

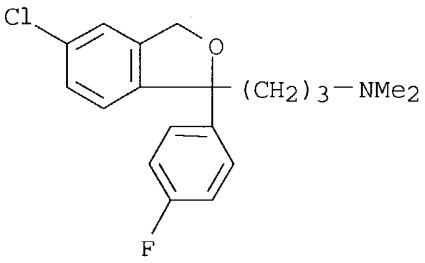
solvent (e.g., sulfolane); the crude citalopram product is optionally subjected to some initial purification and the crude citalopram base is subsequently subjected to a thin- or falling-film distillation process.

IT **64169-39-7 64169-45-5 260066-78-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of high-purity citalopram by cyanidation with purification via thin-film distillation)

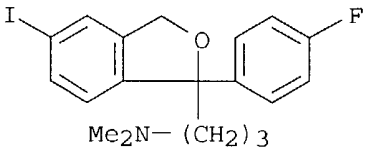
RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 260066-78-2 CAPLUS
CN 1-Isobenzofuranpropanamine, 1-(4-fluorophenyl)-1,3-dihydro-5-iodo-N,N-dimethyl- (9CI) (CA INDEX NAME)



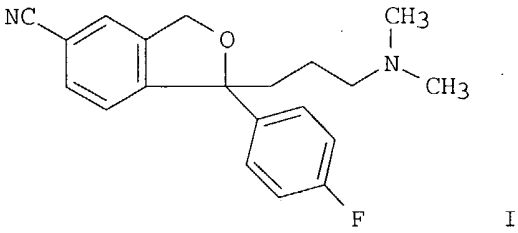
L10 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:472398 CAPLUS
DOCUMENT NUMBER: 135:61224
TITLE: Method for the preparation and purification of citalopram
INVENTOR(S): Villa, Marcos; Sbrogio, Federico; Dancer, Robert
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045483	A2	20010628	WO 2001-DK147	20010307
WO 2001045483	A3	20011227		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NL 1017525	C1	20010426	NL 2001-1017525	20010307
CA 2360303	AA	20010628	CA 2001-2360303	20010307
CA 2360303	C	20030812		
EP 1181713	A2	20020227	EP 2001-913726	20010307
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200201166	T1	20021021	TR 2002-200201166	20010307
JP 2003517484	T2	20030527	JP 2001-546230	20010307
DK 174018	B1	20020422	DK 2001-402	20010308
GB 2357763	A1	20010704	GB 2001-5983	20010312
GB 2357763	B2	20020116		
GB 2359811	A1	20010905	GB 2001-15025	20010312
GB 2359811	B2	20030305		
CZ 292200	B6	20030813	CZ 2001-890	20010312
FR 2812877	A1	20020215	FR 2001-3455	20010314
FR 2812877	B1	20030404		
GR 1003874	B1	20020424	GR 2001-100132	20010316
DE 10112829	C1	20020725	DE 2001-10112829	20010316
CH 691535	A	20010815	CH 2001-545	20010322
BE 1013212	A6	20011002	BE 2001-188	20010322
NL 1018360	C1	20011004	NL 2001-1018360	20010622
BE 1013213	A6	20011002	BE 2001-435	20010626
CH 691998	A	20011231	CH 2001-1411	20010726
ES 2170732	A1	20020801	ES 2001-1762	20010727
AU 744112	B1	20020214	AU 2001-65477	20010827
SE 517623	C2	20020625	SE 2001-3045	20010914
SE 2001003045	A	20020623		
BG 106203	A	20020830	BG 2001-106203	20011210
ZA 2001010179	A	20021211	ZA 2001-10179	20011211
NZ 516298	A	20021220	NZ 2001-516298	20011220
HR 2002000004	A1	20030430	HR 2002-4	20020104
US 2002120005	A1	20020829	US 2002-46126	20020108
US 6455710	B2	20020924		

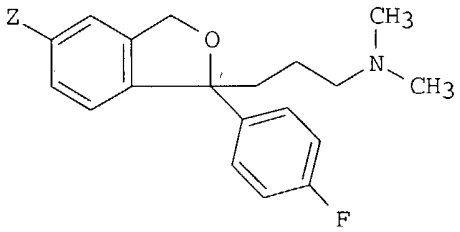
PRIORITY APPLN. INFO.:	DK 2000-1929	A	20001222
	NL 2001-1017525	A	20001222
	WO 2001-DK147	W	20010307
	GB 2001-5983	A3	20010312
	CH 2001-545	A	20010322

OTHER SOURCE(S): CASREACT 135:61224; MARPAT 135:61224

GI



I

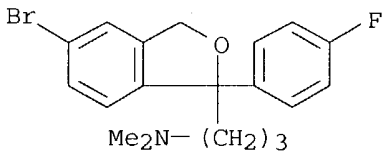


II

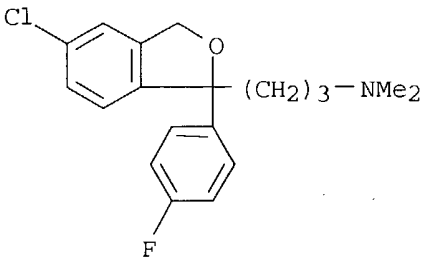
AB A process for the preparation and purification of citalopram (I) is presented in which a benzoisofuran derivative [II; Z = iodo, bromo, chloro, CF3(CF2)nSO2O; n = 0-8] is subjected to a cyanide-exchange reaction with a cyanide source (e.g., cuprous cyanide). The resultant crude citalopram is optionally subjected to some initial purification and subsequently treated with an amide or an amide-like group forming agent (e.g., acetic anhydride), the reaction mixture is then subjected to an acid/base wash and/or crystallization and recrystn. of citalopram in order to remove the amides formed from the crude citalopram mixture, and the resulting citalopram product is optionally further purified, worked up and isolated as the base or a pharmaceutically acceptable salt.

IT **64169-39-7 64169-45-5 260066-78-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for the preparation of citalopram by the cyanidation of)

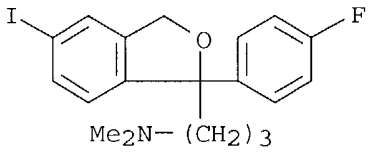
RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



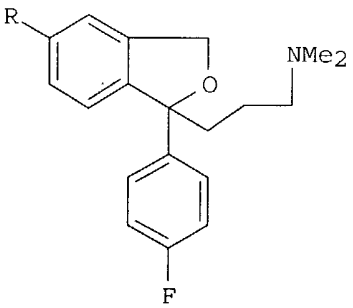
RN 260066-78-2 CAPLUS
CN 1-Isobenzofuranpropanamine, 1-(4-fluorophenyl)-1,3-dihydro-5-iodo-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 22 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:386023 CAPLUS
DOCUMENT NUMBER: 134:353251
TITLE: Method for the preparation of citalopram by nickel-catalyzed cyanation of halo precursors
INVENTOR(S): Petersen, Hans; Rock, Michael Harold
PATENT ASSIGNEE(S): H Lundbeck A/S, Den.
SOURCE: Brit. UK Pat. Appl., 16 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2354240 A1		20010321	GB 2001-1508	19991119
PRIORITY APPLN. INFO.:			DK 1999-921	19990625
			WO 1999-DK643	19991119

OTHER SOURCE(S): MARPAT 134:353251
GI



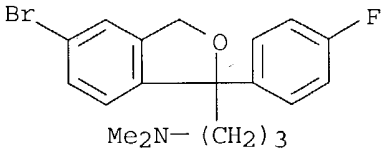
I

AB A method for the preparation of citalopram is presented, comprising the

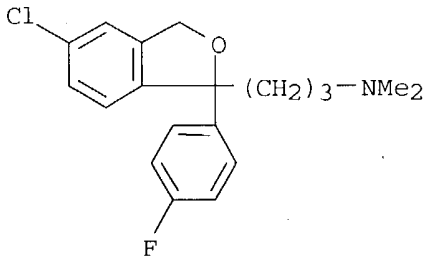
reaction of isobenzofuranpropanamine I, wherein R is Cl or Br, with a cyanide source in the presence of a nickel catalyst and isolation of the corresponding 5-cyano compound, i.e. citalopram.

IT **64169-39-7**, 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- **64169-45-5**, 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for the preparation of citalopram by nickel-catalyzed cyanation of halo precursors)

RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 64169-45-5 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:31487 CAPLUS
DOCUMENT NUMBER: 134:102526
TITLE: Process for the synthesis of citalopram
INVENTOR(S): Bolzonella, Eva; Castellin, Andrea; Nicole, Andrea
PATENT ASSIGNEE(S): Vis Farmaceutici S.p.A., Italy
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002383	A2	20010111	WO 2000-EP6426	20000706
WO 2001002383	A3	20010503		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

IT 99MI1486	A1	20010108	IT 1999-MI1486		19990706
WO 2002004435	A1	20020117	WO 2001-DK481		20010706

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

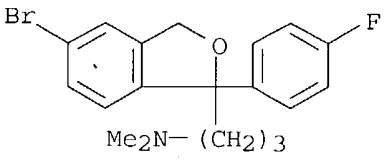
BR 2001006976	A	20020723	BR 2001-6976		20010706
NO 2002001118	A	20020424	NO 2002-1118		20020306
US 2002128497	A1	20020912	US 2002-96149		20020306
PRIORITY APPLN. INFO.:			IT 1999-MI1486	A	19990706
			WO 2000-EP6426	W	20000706
			WO 2001-DK481	W	20010706

AB A new process is described for the synthesis of citalopram characterized by the conversion of 1-(4'-fluorophenyl)1-3-(dimethylaminopropyl)-5-halophthalane in the corresponding Grignard reagent; this intermediate product may be converted into citalopram via intermediate formation of an aldehyde and in the subsequent transformation of the functional group via oxime or hydrazone; or else be converted into citalopram via reaction with compds. containing a cyano group bound to a leaving group. The process described makes it possible to obtain citalopram in high yields, and does not involve the use of drastic conditions of temperature

IT **64169-39-7D**, Grignard compound
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for synthesis of citalopram)

RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

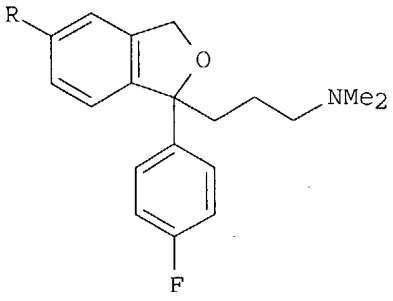
ACCESSION NUMBER:	2000:175646 CAPLUS
DOCUMENT NUMBER:	132:194283
TITLE:	Method for the preparation of citalopram
INVENTOR(S):	Petersen, Hans; Rock, Michael Harold; Svane, Henrik
PATENT ASSIGNEE(S):	H. Lundbeck A/S, Den.
SOURCE:	PCT Int. Appl., 13 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000013648	A2	20000316	WO 1999-DK640	19991122

WO 2000013648		A3	20000713		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
IT 99MI1581		A1	20010115	IT 1999-MI1581	19990715
ES 2169709		A1	20020701	ES 2001-50056	19991025
JP 2003012663		A2	20030115	JP 2002-106016	19991025
EP 1298124		A1	20030402	EP 2002-28326	19991025
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
AU 2000013745		A5	20000327	AU 2000-13745	19991122
GB 2354239		A1	20010321	GB 2001-1504	19991122
GB 2354239		B2	20010606		
GB 2357761		A1	20010704	GB 2001-5182	19991122
GB 2357761		B2	20010905		
EP 1159274		A2	20011205	EP 1999-968622	19991122
EP 1159274		B1	20030326		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 9917368		A	20020305	BR 1999-17368	19991122
AT 9909041		A	20020515	AT 1999-9041	19991122
AT 409961		B	20021227		
TR 200103702		T2	20020621	TR 2001-200103702	19991122
DE 19983487		C1	20020725	DE 1999-19983487	19991122
JP 2002526386		T2	20020820	JP 2000-568457	19991122
JP 3447267		B2	20030916		
AT 235478		E	20030415	AT 1999-968622	19991122
ES 2189699		A1	20030701	ES 2001-50011	19991122
CZ 292198		B6	20030813	CZ 2001-320	19991122
PT 1159274		T	20030829	PT 1999-968622	19991122
ES 2194545		T3	20031116	ES 1999-968622	19991122
NZ 514979		A	20040130	NZ 1999-514979	19991122
SE 2001000193		A	20010425	SE 2001-193	20010124
SE 516690		C2	20020212		
FI 2001000155		A	20010209	FI 2001-155	20010125
ZA 2001008854		A	20020611	ZA 2001-8854	20011026
US 2002077353		A1	20020620	US 2001-12054	20011106
BG 106191		A	20020830	BG 2001-106191	20011207
PRIORITY APPLN. INFO.:				DK 1999-920 A	19990625
				EP 1999-950511 A3	19991025
				JP 2000-571018 A3	19991025
				GB 2001-1504 A3	19991122
				WO 1999-DK640 W	19991122
OTHER SOURCE(S):			CASREACT 132:194283; MARPAT 132:194283		

GI

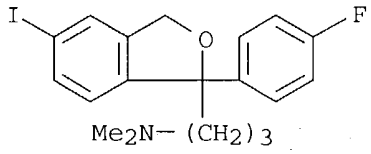


I

AB The title compound [I; R = CN], the well known antidepressant (no data), was prepared by reacting a compound I [wherein R = halo, CF3(CF2)nSO2; n = 0-8] with a cyanide source in the presence of a palladium catalyst and a catalytic amount of Cu+ or Zn2+, or with Zn(CN)2 in the presence of a palladium catalyst.

IT **260066-78-2P 260066-79-3P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method for the preparation of citalopram)

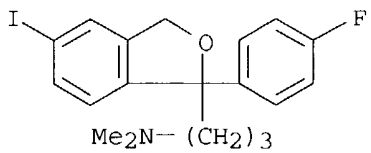
RN 260066-78-2 CAPLUS
CN 1-Isobenzofuranpropanamine, 1-(4-fluorophenyl)-1,3-dihydro-5-iodo-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 260066-79-3 CAPLUS
CN 1-Isobenzofuranpropanamine, 1-(4-fluorophenyl)-1,3-dihydro-5-iodo-N,N-dimethyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

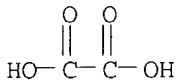
CM 1

CRN 260066-78-2
CMF C19 H21 F I N O

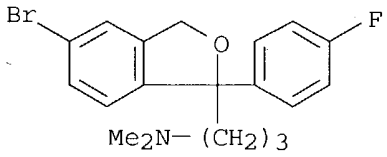


CM 2

CRN 144-62-7
CMF C2 H2 O4



IT **64169-39-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for the preparation of citalopram)
RN 64169-39-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



L10 ANSWER 25 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:743673 CAPLUS
DOCUMENT NUMBER: 130:108685
TITLE: Alteration of central serotonin modifies onset and severity of adjuvant-induced arthritis in the rat
AUTHOR(S): Harbuz, M. S.; Marti, O.; Lightman, S. L.; Jessop, D. S.
CORPORATE SOURCE: Division of Medicine, Department of Hospital Medicine, Bristol Royal Infirmary, University of Bristol, Bristol, BS2 8HW, UK
SOURCE: British Journal of Rheumatology (1998), 37(10), 1077-1083
CODEN: BJRHDF; ISSN: 0263-7103
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

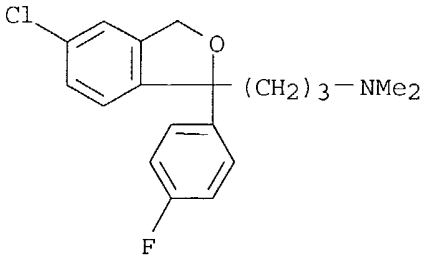
AB Previous studies have determined that depletion of serotonin reduces the severity of hind-paw inflammation in adjuvant-induced arthritis (AA) in the rat. The authors wished to (i) test the hypothesis that this effect may be mediated, at least in part, through a central mechanism and (ii) to investigate further the pro-inflammatory role of serotonin the authors determined whether increasing serotonin using a selective serotonin reuptake inhibitor (SSRI), to increase serotonin availability at the active site of release, would increase inflammation. Serotonin was depleted in the brain of rats with the selective neurotoxin 5'7'-dihydroxytryptamine. Rats were treated with an SSRI on days 10, 11 and 12 following adjuvant injection. Hind-paw inflammation was determined with plethysmometry as an index of severity of inflammation, and brain, pituitaries and blood were collected for assessment of changes in the hypothalamo-pituitary-adrenal (HPA) axis. Serotonin depletion significantly reduced hind-paw inflammation. SSRI-treated animals developed hind-paw inflammation sooner, and the severity was increased compared to vehicle-treated AA rats. The changes in the HPA axis associated with inflammation were partly reversed by this treatment. These data suggest a pro-inflammatory role for central serotonin in this disease model and indicate that treatment with SSRIs may exacerbate the development of inflammation.

IT **64169-45-5**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lu 10-134; central serotonin effect on adjuvant induced arthritis

onset and severity in rat in relation to HPA axis and use of selective serotonin reuptake inhibitor)

RN 64169-45-5 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:448960 CAPLUS

DOCUMENT NUMBER: 129:201594

TITLE: Long-term effects on serotonin transporter mRNA expression of chronic neonatal exposure to a serotonin reuptake inhibitor

AUTHOR(S): Hansen, Henrik H.; Mikkelsen, Jens D.

CORPORATE SOURCE: Department of Neurobiology, H. Lundbeck A/S, Valby-Copenhagen, DK-2500, Den.

SOURCE: European Journal of Pharmacology (1998), 352(2/3), 307-315
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

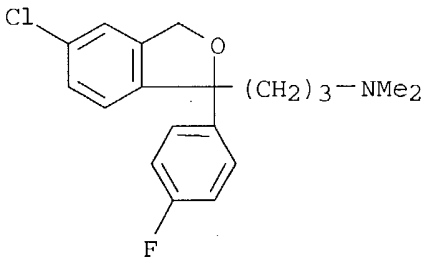
AB Chronic administration of clomipramine or other serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors to neonatal rats produces behaviors that resemble a depressive state in the adult animal, and this model is therefore regarded as a putative animal model of depression. Alterations in the activity of the central 5-HT system are important in understanding the pathophysiol. of depression, and therefore, we examined whether this model was associated with changes in the expression of 5-HT1A receptor, 5-HT1B receptor, and 5-HT transporter mRNA in the dorsal raphe nucleus and the hippocampus. Wistar rats were injected twice daily with the serotonin reuptake inhibitors clomipramine and 5-chloro-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofurane, hydrochloride (Lu 10-134-C) at doses of 15 mg kg-1 or vehicle i.p. from postnatal day 8 for 14 days. Groups of rats (n=10) were either killed the day after the last injection or left undisturbed for 69 days before they were killed. The expression of 5-HT transporter, 5-HT1A receptor, and 5-HT1B receptor mRNA was examined in the dorsal raphe nucleus and in the CA1 of the hippocampus by quant. in situ hybridization histochem. Both compds. resulted in an increase in 5-HT transporter mRNA expression (40% more than vehicle) in the dorsal raphe nucleus the day after the last injection (postnatal day 22). A small but significant increase in 5-HT1B receptor mRNA expression in the CA1 was seen after clomipramine, but not after Lu 10-134-C, probably reflecting clomipramine's affinity for both the 5-HT and noradrenaline transporters as well as for a number of monoamine receptor sites. Levels of 5-HT1A receptor mRNA were unchanged. In contrast, 5-HT transporter mRNA expression in the dorsal raphe nucleus was significantly decreased in the adult after neonatal treatment with either

of the two drugs compared to vehicle. No changes in 5-HT1A receptor and 5-HT1B receptor mRNA expression were observed in any of the regions examined in these animals. The results show that the persistent depressive behavior previously shown in this model is also associated with changes in the expression of 5-HT transporter mRNA. This long-term alteration in gene expression may result from disturbances in 5-HT neurotransmission in the brain of the neonatal animals.

IT **64169-47-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(long-term effects on serotonin transporter mRNA expression of chronic neonatal exposure to serotonin reuptake inhibitor in relation to mental depression)

RN 64169-47-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:26565 CAPLUS
DOCUMENT NUMBER: 128:149485
TITLE: Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: a putative animal model of depression?
AUTHOR(S): Hansen, H. H.; Sanchez, C.; Meier, E.
CORPORATE SOURCE: Pharmacological Research, H. Lundbeck A/S, Copenhagen-Valby, DK-2500, Den.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 283(3), 1333-1341
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

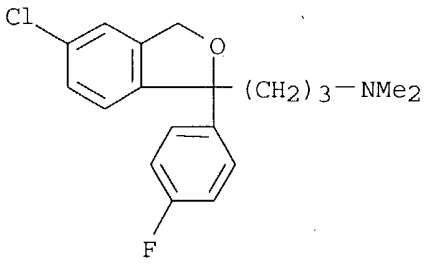
AB Chronic administration of the tricyclic antidepressant clomipramine to neonatal rats from postnatal days 8 to 21 is reported to induce several behavioral changes in adult life, and it may serve as an animal model of human depressive disorder. Findings include increased immobility time in the forced swim test and locomotor hyperactivity in the open field test. Clomipramine is a serotonergic reuptake inhibitor, which suggests that altered development of the serotonergic system could account for the observed behavioral changes in the adult rat. The present study was carried out with a selective serotonin reuptake inhibitor (SSRI) to investigate whether the serotonin system, in particular, is involved in the neonatal

animal model. The substance, Lu 10-134-C (LU), was characterized in monoamine reuptake and receptor binding assays and found to be an SSRI. Rats received LU during postnatal days 8 to 21 (2.5-15 mg/kg b.i.d.), and they were assessed in open field, forced swim and social interaction tests at the age of 4 mo. Behavior of LU-treated rats and saline controls did not differ in the open field and social interaction tests. However, in the forced swim tests LU-treated neonates showed prolonged immobility time compared with saline controls. In conclusion, chronic LU treatment during neonatal life produces long-term changes in the forced swim test, but not in the open field and social interaction tests. The behavioral changes in the forced swim test suggest that the central serotonergic system may be involved in the putative neonatal animal model of depression.

IT **64169-45-5**, Lu 10-134C
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of central serotonergic system in effects of selective serotonin reuptake inhibitor Lu 10-134-C on behavior in neonatal model of depression)

RN 64169-45-5 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1977:561413 CAPLUS

DOCUMENT NUMBER: 87:161413

TITLE: Quantitative structure-activity relationships in a series of selective 5-HT uptake inhibitors

AUTHOR(S): Bigler, Allan J.; Boegesoe, Klaus P.; Toft, Anders; Hansen, Villy

CORPORATE SOURCE: Dep. Synth. Chem., H. Lundbeck and Co. A/S, Copenhagen-Valby, Den.

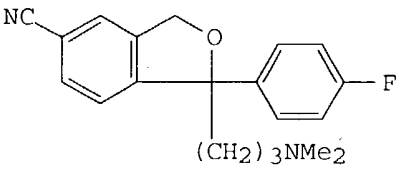
SOURCE: European Journal of Medicinal Chemistry (1977), 12(3), 289-95
CODEN: EJMCA5; ISSN: 0223-5234

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 87:161413

GI

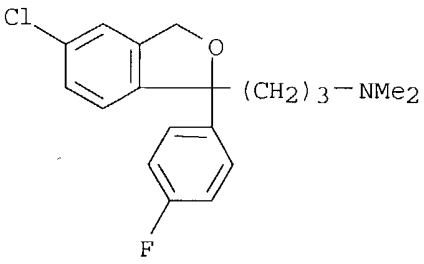


I

AB Fifty-five 1-[3-(methylamino)propyl]- and 1-[3-(dimethylamino)propyl]-1-phenylphthalan derivs. were prepared and tested in vitro for inhibition of 5-hydroxytryptamine [50-67-9] uptake in blood platelets and in vivo for potentiation of 5-HTP syndrome in mice. Quant. structure-activity relations were established, using the methods of Free-Wilson and Hansch. Of several potent compds., Citalopram (I) [59729-33-8] was the most active.

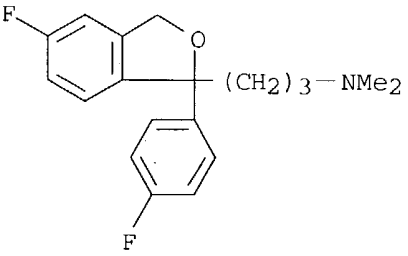
IT **64169-47-7P 64169-54-6P 64372-43-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and hydroxytryptamine inhibition by)

RN 64169-47-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 64169-54-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-fluoro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)

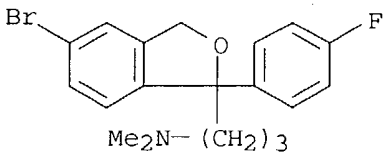


● HCl

RN 64372-43-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

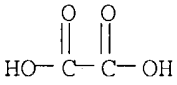
CM 1

CRN 64169-39-7
CMF C19 H21 Br F N O



CM 2

CRN 144-62-7
CMF C2 H2 O4

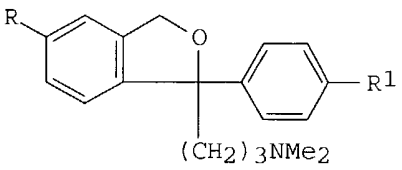


L10 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1977:535040 CAPLUS
DOCUMENT NUMBER: 87:135040
TITLE: Phthalan derivatives
INVENTOR(S): Boegesoe, Klaus Peter; Toft, Anders Stausboell
PATENT ASSIGNEE(S): Kefalas A/S, Den.
SOURCE: Ger. Offen., 30 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2657013	A1	19770728	DE 1976-2657013	19761216
DE 2657013	C2	19851114		
SE 7614201	A	19770715	SE 1976-14201	19761217
SE 429551	B	19830912		
SE 429551	C	19831222		
AT 7609472	A	19800415	AT 1976-9472	19761221
AT 359488	B	19801110		
AU 7721073	A1	19780713	AU 1977-21073	19770105
AU 509445	B2	19800515		
US 4136193	A	19790123	US 1977-757619	19770107
FI 7700073	A	19770715	FI 1977-73	19770111
FI 63754	B	19830429		
FI 63754	C	19830810		
NL 7700244	A	19770718	NL 1977-244	19770112
NL 192451	B	19970401		
NL 192451	C	19970804		
NO 7700109	A	19770715	NO 1977-109	19770113
NO 147243	B	19821122		
NO 147243	C	19830302		
JP 52105162	A2	19770903	JP 1977-1997	19770113
JP 61035986	B4	19860815		
CA 1094087	A1	19810120	CA 1977-269610	19770113
CH 626886	A	19811215	CH 1977-423	19770113
BE 850401	A1	19770714	BE 1977-174098	19770114
DK 7700131	A	19770715	DK 1977-131	19770114
DK 143275	B	19810803		
DK 143275	C	19820118		

FR 2338271	A1	19770812	FR 1977-1079	19770114
FR 2338271	B1	19821105		
AT 7905719	A	19800515	AT 1979-5719	19790827
AT 360001	B	19801210		
AT 7905720	A	19800515	AT 1979-5720	19790827
AT 360002	B	19801210		
CH 632258	A	19820930	CH 1981-3574	19810601
CH 632259	A	19820930	CH 1981-3575	19810601
PRIORITY APPLN. INFO.:			GB 1976-1486	19760114
			AT 1976-9472	19761221
			CH 1977-423	19770113

GI



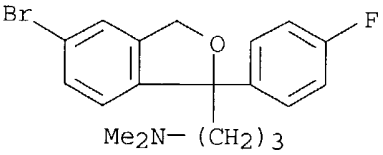
I

AB Phthalans I (R = Cl, Br, CF3, F, CN, COEt; R1 = Cl, F, Br, CN) were prepared Thus, 5-bromophthalide was treated with 4-ClC6H4MgBr, 4,2-Br(HOCH2)C6H3COC6H4Cl-4 treated with Me2N(CH2)3MgCl, and 4,2-Br(HOCH2)C6H3C(OH)(C6H4Cl-4)(CH2)3NMe2 cyclized with H3PO4 to give I (R = Br, R1 = Cl), which had ED50 in the tryptophan potentiation test of 4.6 mg/kg i.p.

IT **64169-39-7P 64169-45-5P 64197-06-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antidepressant activity of)

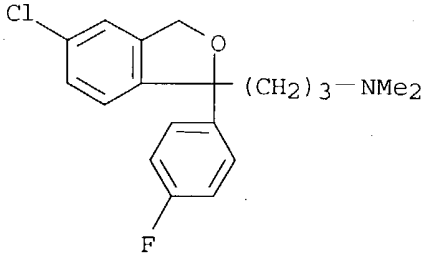
RN 64169-39-7 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)

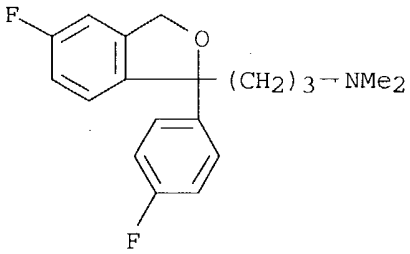


RN 64169-45-5 CAPLUS

CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



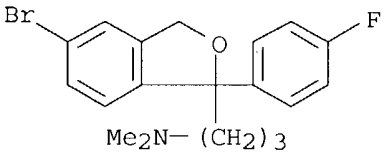
RN 64197-06-4 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-fluoro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl- (9CI) (CA INDEX NAME)



IT **64169-40-0P 64169-46-6P 64169-47-7P 64169-54-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 64169-40-0 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-bromo-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, ethanedioate (9CI) (CA INDEX NAME)

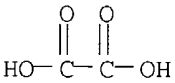
CM 1

CRN 64169-39-7
CMF C19 H21 Br F N O



CM 2

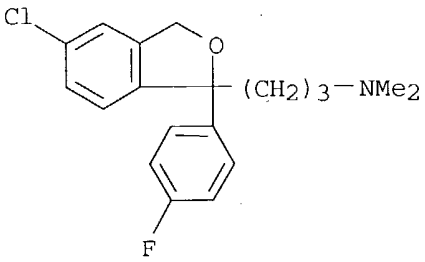
CRN 144-62-7
CMF C2 H2 O4



RN 64169-46-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, ethanedioate (9CI) (CA INDEX NAME)

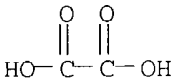
CM 1

CRN 64169-45-5
CMF C19 H21 Cl F N O

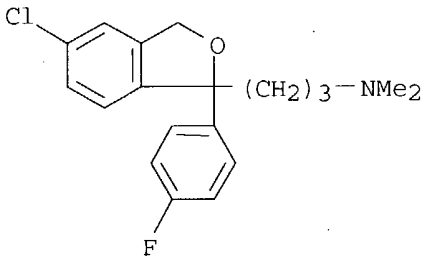


CM 2

CRN 144-62-7
CMF C2 H2 O4

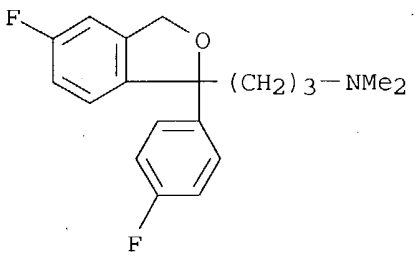


RN 64169-47-7 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-chloro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)



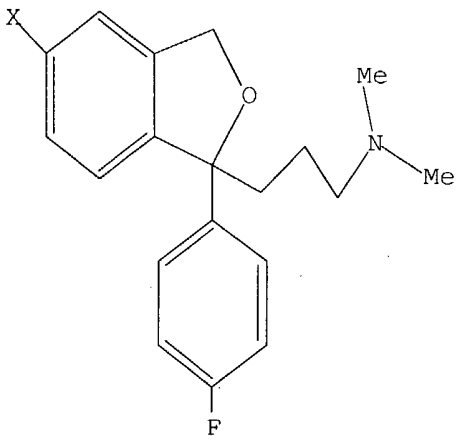
● HCl

RN 64169-54-6 CAPLUS
CN 1-Isobenzofuranpropanamine, 5-fluoro-1-(4-fluorophenyl)-1,3-dihydro-N,N-dimethyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

```
=> d his

     (FILE 'HOME' ENTERED AT 10:19:47 ON 22 SEP 2004)

     FILE 'CAPLUS' ENTERED AT 10:20:23 ON 22 SEP 2004

     FILE 'REGISTRY' ENTERED AT 10:20:42 ON 22 SEP 2004
L1              STRUCTURE UPLOADED
L2            0 S L1
L3           13 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 10:21:34 ON 22 SEP 2004
L4           29 S L3
L5            1 S CITALOPRAM FREE BASE
L6         1822 S CITALOPRAM
L7           32 S CRYSTALLINE FREE BASE
L8            0 S L6 AND L7
L9            0 S L4 AND L7
L10          29 S L4 OR L5

=> d l1
L1 HAS NO ANSWERS
L1               STR
```



G1 H,O,N

G2 X,NH

Structure attributes must be viewed using STN Express query preparation.

=>